# PERSON-ORIENTED PERSPECTIVES IN NEUROLOGY

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SUMMARY – Person-oriented medicine is characterized by a holistic approach in patient management that embraces physical, psychological, social and spiritual aspects of health and disease. It responds to the needs of patients and health care workers to form an effective therapeutic relationship based on trust, empathy, compassion and responsiveness to the individual needs of a patient. Person-oriented perspectives in neurology include active collaborative partnership between a physician and a patient, and intuitive perception, which has a neurobiological correlate in the human mirror neuron system, thus expressing a considerable impact on the quality of the physician's diagnostic and therapeutic activities. On the other hand, personalized approach in medicine implies integration of clinical information and personal genotyping. Personalized neurology provides gene-based preclinical prediction of disease with improved risk assessment, early detection of disease and targeted intervention. The combination of personalized approach and clinical information accelerates the translation of genetic discoveries into clinical practice, which ultimately results in improved health care system. Person-oriented perspectives contribute significantly to the growing pluralism of medical science and provide a greater humanization of medicine, individualized treatment and autonomy during therapeutic processes.

Key words: *Individualized medicine; Nervous system diseases – diagnosis; Nervous system diseases – therapy; Genetic testing*

## Brief History and Conceptual Differences in Person-Oriented and Personalized Medicine

Person-oriented medicine (person-centered medicine) represents a new concept in medicine based on the holistic approach towards patient that includes the totality of person's health, and collaborative partnership between the doctor and the patient, based on mutual understanding with proactive healing approach. Although the core of medical profession has always been clinical skill, the quality of communication within the health care team is crucial to person-oriented medicine. Person-oriented medicine takes into consideration physical, psychological or spiritual components, all embraced in a single individual, thus emphasizing the heterogeneity of patients, diseases and individually adjustable treatment options. The concept of person-centered medicine stems from the traditional, complementary and alternative medicine[1-4]. Traditional, complementary and alternative medicine is essential to the development and implementation of person-oriented medicine. The principal contribution of traditional medicine is holistic understanding of the human being as a unique bio-psycho-spiritual entity in health and illness, in diagnosis and treatment[5,6]. Person-oriented medicine moves the patient from being passive recipient of health care to being informed and competent participant at an individual, organizational and community level. An effective therapeutic relationship based on trust and empathy, compassion and responsiveness to individual needs is the key step for establishment of person-oriented medicine[7-9]. In traditional medicine,

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the doctor-patient relationship was perceived as social interaction typical for the state of addiction, implying dependence of patients on the expert opinion of the doctor, with the patient having a subordinate role. The paternalistic relation, where the doctor made all decisions related to patient is becoming a history, thus the doctor and his patient are establishing a collaborative partnership through qualitative communication. The increasing number of health care institutions recognize the importance of person-oriented medicine, bringing forward personalization, prevention and prediction in medicine, incorporating the complexities and the psycho-spiritual aspects of the human being and of the sole medical act. The origins of the person-centered medicine might be tracked back in psychiatry and psychosomatic medicine, in Charcot and Freud's contribution on mind and body relationship and understanding of the subconscious in the human behavior. Modern psychosomatic medicine thus resulted from the confluence of disease psychogenesis and holism, although contemporary perspectives on the relationship between the patient and the doctor originated from models based on the passivity-activity relationship[6,11]. The most prominent roots of the person-centered trends in medicine can be traced back to 1950, to the origins of the World Psychiatric Association that merged humanism and science through various collaborations with international health organizations, including the World Medical Association and the World Health Organization[10-12]. The extension of the person-centered medicine from psychiatry to medicine led to the foundation of the International Network of Person-centered Medicine and recent research projects of person-centered health care[13]. Person-oriented medicine is widening the paradigm in medicine and health by following the increasing demand for holistic medical approach and reintegration of an individual being fragmented by different medical specializations. It contributes to the growing pluralism of medical science, adding to the paradigm of personalized medicine.

On the other hand, personalized medicine is a novel model evolving in health care, which is driven by joint individual clinical, genetic, and environmental information. The goal of personalized medicine is to improve treatment outcomes and reduce adverse events that matter to the clinician and the patient. The concept of personalized medicine includes selective genotype-based prescription of medications to individuals for whom the medication should be safe and effective[14,15]. Personalized medicine was defined by Francis Collins, head of the Human Genome Project as "using information about a person's genetic map to tailor strategies for the detection, treatment, or prevention of disease". The Human Genome Project allowed a new vision of genomic or personalized medicine customizing each treatment for utmost efficacy in an individual patient. Ever since it was completed, back in 2001, biomedicine research has been mostly focused on genetic markers, sections of DNA, like short tandem repeats or single-nucleotide polymorphisms which made genome-wide association studies as a major source of information in modern genetics and genomics[16,17]. Genomic approach provides complementary insights into personalized medicine by combining clinical information with genotyping and predicting risk of diseases, classification of diseases on molecular basis and creating an individualized treatment. It aims for the clinical, genetic, imaging or immunologic biomarkers that provide better stratification of patients[16-18]. Biomarkers have a promising value in the diagnostics and stratification of disease stages, prediction of disease course, treatment selection and prognosis of treatment outcome. However, the greatest opportunity for personalized medicine lies in the gene-based pre-symptomatic prediction of disease with improved risk assessment for early detection and targeted intervention. The greatest area of clinical application of personalized medicine lies in pharmacogenomics, where the ultimate goal is to maximize therapeutic response and minimize drug toxicity, and the most common use of genomics is the assessment of drug response within individual, based on genotyping test for the analysis of cytochrome P450 gene and its polymorphisms[19-21]. Genotyping is also used within pharmacotherapy for drug selection and dosage. On the other hand, the greatest limitation in personalized medicine is inability to accurately predict individual risk for the patient, which might be resolved only by integrating all forms of personal information from preclinical and clinical stages[18]. Although traditional medicine may concede to a more convenient approach in health care, understanding personal complaints and needs and the environment

of the patient may be easily translated into both person-oriented and personalized medicine.

## Person-Oriented Perspectives in Neurology

Physician-patient relationship and medical environment are known to be important in the treatment process and have a considerable impact on treatment outcome. When therapy is administered, medical environment might determine the outcome of treatment by inducing expectations of clinical benefit[22,23]. The psychosocial background may act through complex cognitive factors, such as anticipation and expectation of an outcome. Doctor-patient relationship often includes mutual intuitive understanding and perception, which has a neurobiological correlate in the human mirror neuron system. Mirror neurons are essential neurobiological basis for human ability of empathy with others and for intuition. The system of mirror neurons in the observer's brain is capable of simulating and imitating a process, motor or somatosensory experience, that takes place in the body of the other observed individual. Respecting intuitive processes and making them useful in the physician-patient collaborative relationship is the goal of person-oriented neurology. Thus, empathic listening or medical interview by a physician provides a framework for understanding the mind-body relationship[24-27]. Neurological disorders often have an intensive emotional superposition and symptoms often cannot be explained by any known mechanism. Emotions are associated with accompanying neurobiological processes and may have considerable impact on the healing process. The relationship between neurological disorders and psychiatric symptoms ranges from coincidental occurrence to a direct causal role in the development of psychiatric disturbances[28,29]. Psychosomatic treatment that comprises individual and group psychotherapy, behavioral techniques and psychopharmacology with conventional medication is particularly helpful in the presence of mood disturbances or psychiatric illness, illness denial or hypochondriasis, or in patients with impaired quality of life that is not justified by the medical condition[30]. Neurology is dealing with various diseases and syndromes, some of which are significant causes of morbidity and mortality worldwide. Nevertheless, in neurology, as in other fields of medicine, there is still a trend to classify patients according to their diagnosis, thus treating a disease rather than a patient. In the following section, a short review of the most common neurological disorders is presented as a reminder of the importance of intuitive perception when following the idea of individualized, patient-oriented approach in neurology.

## Person-Oriented Perspectives in Common Neurological Disorders

Cognitive modulation of pain plays an important role in pain processing. Although pain is subjective, experience of pain depends upon physiological, psychological and social factors[31]. Sensory perception has an important role in pain sensation and cognitive aspect of pain is a complex neuropsychological phenomenon. A number of patients exhibit hypersensitivity to external stimulation and hyper-anxiety for pain sensation. Traditionally, pain is divided into acute and chronic pain. Chronic pain stems from dysfunction in neuronal pathways and central sensitization through continuous activation of peripheral neurons. It is often accompanied by depression, possibly due to common biochemical characteristics involving the noradrenaline and serotonin system. Depression often manifests with chronic pain, thus pain is more acceptable. But, it often has negative impact on the quality of life; it increases the intensity and duration of pain and limits daily activities of patients. Recent findings show that psychosocial pain related to social exclusion, social loss and empathy causes activation of the brain area also activated during physical pain. The bio-psycho-social model of pain includes somatic component such as localization, intensity and quality; psychological component such as mood and affection; cognitive process and social component such as activity of daily living, work ability and interpersonal relationships, hence implying a multidisciplinary approach in medical treatment of pain[32,33]. Placebo administration, along with verbal suggestions of analgesia, might reduce pain by expectation and conditioning mechanisms. A future challenge for placebo research is the possible application in different diseases and clinical settings[34].

Another neurological disorder is tension type headache usually defined as a psychogenic headache, or a headache without the organic basis. It has been suggested that the term should be limited to patients where headache is the main symptom of a psychiatric

disorder. However, psychiatrically caused headache was not recognized as a form of secondary headache. Instead, such headache was considered a form of tension type headache, often called neurotic or stress headache that might be perceived as a physical expression of psychic tension. It might also be caused by continuous stress, depression or anxiety. The etiology of psychogenic headache includes inner conflict enclosed inside the psychological structure of personality. It might be one of the hallmarks of converse neurosis that originates from early phases of personal development and may represent the subconscious desire for destruction of an object or a person[31,35]. When tension type headaches occur as a symptom of another medical condition, it will generally subside when the underlying condition is treated successfully. Furthermore, stress is an important etiologic factor in another type of primary headache, i.e. migraine. Migraine occurs more often in intelligent, ambitious and sensitive subjects with too many occupations and tasks that are limited by timelines. It might originate from insomnia, lack of relaxation, or misbalance of a personal lifestyle and the person is unable to relax due to some obstacle subconscious mechanism.

Behavioral, psychotic and anxiety disorders are common in epilepsy patients. The possible common neuropathology includes genetic predisposition, although common relationship is controversial[36-38]. The psychiatric comorbidities include psychosis, anxiety and depression[37,38]. Psychosis that accompanies temporal lobe epilepsy and postictal psychosis is present in many epilepsy patients. Further on, depression might be observed in complex partial epilepsy, and anxiety often accompanies ictal phenomena and interictal symptoms[39]. Depression occurs frequently in patients with temporal lobe epilepsy and significantly influences their lowered neuropsychological functions. Poor psychosocial condition and social stigma are additional predictors of depression in epilepsy patients, resulting in social discrimination and undermining the treatment of the disease. Hence, it is important to establish a collaborative relationship with the patient and family members, and carefully evaluate the factors that might predispose development of depression and stigmatization, which often have negative impact on the quality of life of epilepsy patients. Removing the stigma denotes rising of public and professional awareness and changing the legislation that sometimes reinforces discrimination of epilepsy patients.

Psychiatric disorders in Parkinson's disease patients include depression, anxiety, sleep disorders, obsessive-compulsive disorders and psychosis, some of which might occur as a result of impaired medical treatment[40,41]. Psychiatric disorders have significant clinical consequences and substantial impact on the activities of daily living in Parkinson's disease patients. In nearly half of Parkinson's disease patients, depression occurs in early and late stage of the disease. It often accelerates cognitive impairment, progression of motor deficit, and has negative influence on the quality of life. Parkinson's disease patients with depression exhibit lower brain activity levels in the orbitofrontal cortex, diminishing their ability to experience pleasure and to anticipate future rewards. Concomitant disorders in Parkinson's disease patients include mild cognitive impairment, often accompanied by psychomotor inhibition, sleep disorders and loss of concentration, and sometimes suicidal behavior[41]. Inappropriate medical treatment also results in increased dependence, thus personalized medical treatment provides reduction of complications due to inadequate medical treatment.

There is a considerable impact of emotional, physical and environmental stressful events that might influence the etiology of multiple sclerosis and its progression. Chronic stress might increase the risk of the body autoimmune response. Much is discussed about the organic etiology of multiple sclerosis that embraces autoimmune and endocrine disorders, iatrogenic and genetic factors and the reactive etiology of multiple sclerosis[21,42]. The comorbidity of cognitive disorders and mood disorders is actually featured in multiple sclerosis. Mood disorders like depression and anxiety are often recognized in multiple sclerosis and might influence cognitive functions and actually worsen the genuine organic deficit by the loss of memory and executive functions. Distinguishing the reactive etiology and biological basis of the disease might be difficult; hence neuropsychological testing might be needed.

Stressful psychosocial context with diminished social support has an important role in the etiology of cerebrovascular incidents. Psychosocial risk factors for cerebrovascular incidents might be increased in certain personality types that are characterized with anger

and impatience in stressful situations. Risk factors for stroke are often classified as non-modifiable (age, gender, race and genetic heritage) and modifiable (smoking, stress, physical inactivity, metabolic syndrome), but personality adjustment such as synchronization of ideal and real ego might be necessary in reducing the risk of stroke[43]. Personality and behavioral changes related to post-stroke period comprise neurobehavioral changes such as aphasia and cognitive deficit, dissociation of emotions, anxiety, depression, emotional incontinence, psychosis and obsessive-compulsive disorder. Understanding the neurobehavioral changes after stroke is the paradigm for understanding the clinical consequences of cerebral lesions.

## Personalized Neurology and Neurogenetics

Neurological disorders are a major health problem and impose a large health care cost associated with treatment of uncertain cost-effectiveness. The concept of personalized neurology includes safe and effective treatment decisions for neurologic disorders based on individual genotyping and personalized dosing[43,44]. Genetics accounts for variability in drug disposition, but a large proportion of population may be defective in the gene responsible for drug metabolism. The genetic background of a patient could be used as a personalized biomarker. However, genetic markers in neurology have not proven to be of great use because of the large number of genetic polymorphisms. Polymorphisms in the genes affecting pharmacodynamics response or metabolism are often associated with a lack of therapeutic effect. One of the examples of applied genomic medicine is individualized application of anticoagulation therapy with warfarin in the prevention of cerebral and systemic thromboembolism. Polymorphisms of VKORC1 gene that affect pharmacodynamics response to warfarin or polymorphisms of CYP2C9 gene that affect warfarin metabolism are associated with a lack of therapeutic effect of warfarin[45]. Neurogenetics and DNA sequencing have allowed broader understanding of the neurobiological perspectives of human behavior and molecular pathways involved in specific brain functions. Sustainment of gene structure, expression of neuropeptides oxytocin and vasopressin and diversity in the genetic regulation might contribute to variations in social behavior by altering brain functions. Therapeutic potential of modulating the oxytocin pathway has potential for development of effective treatment of behavioral disorders[46,47]. On the other hand, the research into predictive biomarkers in neurology may lead to promising results in the field of neuroimmune disorders, demyelinating and neurodegenerative diseases. Established biomarkers in neurology include antibodies against acetylcholine receptor in myasthenia gravis, and detection of anti-Hu and anti-Yo antibodies in paraneoplastic disorders. In demyelinating diseases, aquaporin 4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) have been recognized as antibody targets. Antibodies against AQP4 are associated with the clinical spectrum of neuromyelitis optica that is related to a more aggressive course than general multiple sclerosis, and responds better to immunosuppressive than to immunomodulation therapy. MOG antibodies might help in differentiating viral and autoimmune encephalitis and separating monophasic acute disseminated encephalomyelitis and pediatric multiple sclerosis. The role of MOG antibodies in adult multiple sclerosis is still speculative and further research is needed for the utility of MOG antibodies for prognosis or classification of adult multiple sclerosis patients. Progress on predictive biomarkers to guide disease-modifying therapy in multiple sclerosis and minimize side effects has been disappointing despite extensive efforts[48]. Research of neurodegenerative disorders recognized that APOE might have varying effects in different neurodegenerative diseases[43,44]. Genomics offers opposite insights into personalized neurology by combining clinical information with genotyping and forecasting the risk of disease and generating personalized treatment; however, despite extensive research, only a few biomarkers have made their way into clinical practice.

## Conclusion

Summarizing the facts about person-oriented and personalized perspectives in medicine, one can easily determine the advantages of personalized approaches. Person-oriented and personalized neurology both put the patient and individual genetic background in the spotlight of the health care system, choosing mutual collaborative relationship and individualized approach over submissive, conditioned physician-patient relationship and traditional algorithmic treatments. Collaborative partnership and intuitive perception feature

person-oriented neurology and have a considerable impact on the quality of the physician's diagnostic and therapeutic activities. Personalized neurology provides optimal therapy for the patient, increased safety, reduction of time consuming treatments, cost treatment reduction and reduction of costs in health policy. Future perspectives in neurology are oriented towards conjunction of genomic and clinical data and translation of genetic discoveries into clinical practice, which will hopefully result in cost-effective treatment and improved health care.

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Sažetak

## PERSPEKTIVE MEDICINE USMJERENE PREMA OSOBI U NEUROLOGIJI

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Medicinu usmjerenu prema osobi obilježava holistički pristup bolesniku, koji objedinjuje fizičke, psihičke, socijalne i duhovne aspekte zdravlja i bolesti. Medicina usmjerena prema osobi prilagođena je potrebama bolesnika i zdravstvenih djelatnika, a za ostvarenje učinkovitog terapijskog odnosa temeljenog na povjerenju, empatiji, suosjećanju te odgovoru na individualne potrebe bolesnika. Perspektive u neurologiji usmjerene prema osobi uključuju aktivnu suradnju i partnerstvo između liječnika i bolesnika te intuitivnu percepciju koja ima neurobiološku poveznicu u ljudskom sustavu zrcalnih neurona te značajan utjecaj na kvalitetu dijagnostičkih i terapijskih aktivnosti liječnika. S druge strane, personalizirani pristup u medicini podrazumijeva objedinjavanje kliničkih podataka i osobnu genotipizaciju. Personalizirana neurologija omogućava predkliničku genetsku analizu ishoda bolesti, poboljšanu procjenu rizika, rano otkrivanje bolesti i ciljanu intervenciju. Kombinacija personaliziranog pristupa i kliničkih podataka ubrzava prijenos genetskih otkrića u kliničku praksu, što u konačnici rezultira poboljšanjem zdravstvenog sustava. Neurološke perspektive usmjerene prema osobi značajno doprinose rastućem pluralizmu medicinskih znanosti te omogućuju veću humanizaciju medicine, individualizirano liječenje i autonomiju tijekom terapijskih postupaka.

Ključne riječi: *Individualizirana medicina; Neurološke bolesti – dijagnostika; Neurološke bolesti – terapija; Genetičko testiranje*